

Amendments to the Specification:

Please replace the paragraph at page 3, lines 15-24, with the following paragraph:

To achieve these objectives, in one aspect of the invention, a chimeric anti-idiotype antibody or fragment thereof which specifically binds to the idiotype region of an anti-CEA monoclonal antibody is provided, comprising the rWI2 light chain and heavy chain variable regions, or silent mutations thereof. In a preferred embodiment, the heavy chain variable region comprises the ratWI2VK rWI2VH sequence shown in Figure 1 (SEQ ID NO:18) and the light chain variable region comprises the RatWI2VK rWI2VK sequence shown in Figure 2 (SEQ ID NO:22).

Please replace the paragraph at page 3, lines 25-33, with the following paragraph:

In another aspect of the invention, a humanized anti-idiotype antibody or fragment thereof which specifically binds the idiotype region of an anti-CEA monoclonal antibody is provided, comprising rWI2 CDR regions and humanized FR regions. In a preferred embodiment, the heavy chain variable region comprises the KOLWI2VH-1 (SEQ ID NO:19) or the KOLWI2VH-2 (SEQ ID NO:20) sequence/shown sequence shown in Figure 1 and the light chain variable region comprises the REIWI2VK (SEQ ID NO:24) or the REIWI2VKRS (SEQ ID NO:23) sequence shown in Figure 2.

Please replace the paragraph at page 4, lines 1-14, with the following paragraph:

In another aspect of the invention, an isolated polynucleotide encoding the heavy chain or the heavy chain variable region of a chimeric or humanized antibody or antibody fragment which specifically binds the idiotype region of an anti-CEA monoclonal antibody is provided,

comprising sequences enclosing at least two rWI2 heavy chain CDRs, selected from the group of CDRs consisting of:

the complementary determining region-1 (CDR-1) sequence NYWMT(SEQ ID NO:1),

the complementary determining region-2 (CDR-2) sequence SITSTGGTYHAESVKG (SEQ ID NO:2), and

the complementary determining region-3 (CDR-3) sequence DDYGGQSTYVMDA (SEQ ID NO:3).

Please replace the paragraph at page 4, lines 15-27, with the following paragraph:

In another aspect of the invention, an isolated polynucleotide encoding the light chain or the light chain variable region of a chimeric or humanized antibody or antibody fragment which specifically binds the idiotype region of an anti-CEA monoclonal antibody is provided, comprising sequences enclosing at least two rWI2 CDRs, selected from the group of CDRs consisting of:

the complementary determining region-1 (CDR1) sequence RASQDIGNYLR (SEQ ID NO:4),

the complementary determining region-2 (CDR2) sequence GATNLAA (SEQ ID NO:5), and

the complementary determining region-3 (CDR3) sequence LHHSEYPYT (SEQ ID NO:6).

Please replace the entire section labeled Description of the Figures with the following section:

Figure 1 shows the design of the hVH. The rVH is shown aligned with KOL, and with the designed ~~KOLW2VH-1~~ KOLWI2VH-1 (SEQ ID NO:19) and 2 (SEQ ID NO:20) sequences. Dashes indicate that the sequence matches at that position in the rWI2VK sequence (SEQ ID NO:22). Narrow boxes indicate positions where the rat aa was retained in the humanized FR

sequences. Note that the KOLWI2VK-1 (SEQ ID NO:19) sequence contains an extra rat aa, when compared with KOLWI2VK-2 (SEQ ID NO:20), at position 5. CDRs are indicated by wider boxes ~~and are labeled above the respective box as CDR1 to CDR3.~~

Figure 2 shows the design of hVK. The RATWI2VK rWI2VK (SEQ ID NO:22) sequence is shown aligned with REI, and with the designed REIWI2VK (SEQ ID NO:24) and REIWI2VKRS (SEQ ID NO:23). Dashes indicate that the sequence matches at that position in the RATWI2VK rWI2VK (SEQ ID NO:22) sequence. Narrow boxes indicate positions where the rat aa was retained in the humanized FR sequences. As indicated, four rat aa residues were retained in the FR regions. CDRs are indicated by wider boxes ~~and are labeled above the respective box as CDR1-3.~~

Figure 3A-3B shows the polynucleotide sequence for the hWI2 heavy chain variable region (SEQ ID NO:25). The PCR primers employed and the synthesized oligo K and oligo L described in the text are indicated. A single aa letter code is given below the polynucleotide sequence to represent the translation product. The CDRs (SEQ ID NOs:1, 2 and 3) are underlined on the protein sequence.

Figure 4A-4B shows the polynucleotide sequence for the hWI2 light chain variable region (SEQ ID NO:27). The PCR primers employed and the synthesized oligo M and oligo N described in the text are indicated. A single aa letter code is given below the polynucleotide sequence for the translation product. The CDRs (SEQ ID NOs:4, 5 and 6) are underlined on the protein sequence.

Figure 6 shows the nucleic acid sequence for the variable region of rWI2 light chain (SEQ ID NO:29). The protein translation product is indicated below the nucleic acid sequence,

using one letter aa code (SEQ ID NO:29). The aa residues representing CDRs 1-3 (SEQ ID NOs:4, 5 and 6) are underlined and labeled.

Figure 7 shows the nucleic acid sequence for the variable region of rWI2 heavy chain (SEQ ID NO:31). The protein translation product is indicated below the nucleic acid sequence, using one letter aa code (SEQ ID NO:31). The aa residues representing CDRs 1-3 (SEQ ID NOs:1, 2 and 3) are underlined and labeled.

Please replace the paragraph at page 17, lines 11-22, with the following paragraph:

Genes encoding the antibodies of the invention are introduced via expression vectors into a host cell, for expression. In a preferred embodiment, the genes for both the light and heavy genes ~~are introduced~~ are introduced in a single expression vector, which is introduced in a host cell. The expression vectors generally contain drug markers for selection of the transformed cell. A drug marker can furthermore be used to amplify the copy number of nearby genes, resulting in a clone overexpressing the antibody. For example, a vector expressing the light and heavy chains of cWI2 or hWI2 were introduced into SP2/0 cells on vectors containing the DHFR gene. The original clones were amplified after selection by growth on methotrexate (MTX).

Please replace the paragraph at page 17, lines 23-34, with the following paragraph:

It should be understood that alternative ways to coexpress the light and heavy chain genes are feasible. A skilled artisan could consider other selection regimens, introduction of both the light and heavy chain genes on one plasmid or cotransformation with separate vectors encoding ~~the light~~ the light and heavy genes, and transfection of other cell lines. Furthermore, expression of the antibody in yet other systems is possible. For example, expression could occur in yeast. Alternatively, baculoviruses can be engineered with the light and heavy genes and expressed in cultured cells, or used to infect an insect.

Beginning at page 21, line 28, and continuing through page 22, line 7, please replace the sequence information with the following:

(RCH1) 5'-GAC GTA TAC CTG TGG TTT TCT G 3' (SEQ ID NO:7),
(RVH-1BACK) 5'-AGG TSM ARC TGC AGS AGT CWG G-3' (SEQ ID NO:8), and
(RVH-1FOR) 5'-TGA GGA GAC GGT GAC CGT GGT CCC TTG GCC CC-3' (SEQ ID NO:9),

where S = G + C; M = A + C; R = A + G; and W = A + T, and

(RK1) 5'-GGA TGA TGT CTT ATG AAC AA-3' (SEQ ID NO:10),
(RVK-1BACK) 5'-CCA GTT CCG AGC TCG TGC TCA CCC AGT CTC CA-3' (SEQ ID NO:11),
(RVK-2BACK) 5'-CCA GTT CCG AGC TCC AGA TGA CCC AGT CTC CA-3' (SEQ ID NO:12),
(RVK-3BACK) 5'-CCA GAT GTG AGC TCG TGA TGA CCC AGA CTC CA-3' (SEQ ID NO:13),
(RVK-4BACK) 5'-CCA GAT GTG AGC TCG TCA TGA CCC AGT CTC CA-3' (SEQ ID NO:14),
(RVK-5BACK) 5'-CCA GTT CCG AGC TCG TGA TGA CAC AGT CTC CA-3' (SEQ ID NO:15), and
(RVK-1FOR) 5'-GTT AGA TCT CCA GCT TGG TCC C-3' (SEQ ID NO:16).

Please replace the paragraph at page 22, lines 9-28, with the following paragraph:

First-strand cDNA was prepared from total RNA isolated from WI2 hybridoma using random hexamers as the annealing primers. RCH1 (which anneals to the rat IgG1 CH1 domain) and RVH-1BACK (which anneals to rat 5' VH region) were tried as a primer pair to PCR-amplify and isolate the VH sequence from the first-strand cDNA template, using standard protocols. However, no PCR product was obtained. Unexpectedly, the RCH1 primer, in conjunction with the Orlandi primer VH1BACK (5'-AGG TSM ARC TGC AGS AGT CWG G-3') (SEQ ID NO:8) produced a PCR product of the expected size. The PCR-amplified VH sequence was digested with the restriction enzymes PstI/BstEII and subcloned into the

corresponding sites of the heavy chain staging vector, VH_pBS. See Leung *et al.*, *Hybridoma* 13: 469 (1994). Six individual clones were sequenced and confirmed to be identical to each other. RVH-1FOR which anneals to rat 3' VH region and RVH-1BACK also produced a PCR product of the expected size, which was not further analyzed. Figure 7 shows the sequence of the heavy chain variable region (SEQ ID NO:31).